

NORTHWEST REGIONAL



HAWAII PRACTITIONER'S MANUAL



NEWBORN SCREENING PROGRAM

THE NORTHWEST REGIONAL NEWBORN SCREENING PROGRAM PRACTITIONER'S MANUAL

HAWAI`I

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INTRODUCTION

Mass screening of newborn infants is an important preventive public health strategy to detect treatable disorders that can lead to mental and growth retardation, other physical disabilities, and even death. The cost of not diagnosing one of these conditions, both in human suffering and financial terms, is immense because early diagnosis and treatment of these disorders can result in normal growth and development, minimize health problems associated with these disorders, and provide important genetic information for families.

Babies with these conditions appear normal at birth. It is only with time that the biochemical abnormality affects the baby's health and development. By the time clinical symptoms appear, the damage may be permanent.

The goal of the Northwest Regional Newborn Screening Program (NWRNBSP), which includes Oregon, Idaho, Nevada, Alaska, and Hawai'i, is to identify all affected infants before damage can occur. To do so, every baby must be screened.

Newborn Screening in Hawai'i

In Hawai'i, newborn screening for phenylketonuria (PKU) began in 1966. In 1983, screening for congenital hypothyroidism was added. The Hawai'i Newborn Metabolic Screening Program was established within the Department of Health in 1985 in order to track and follow-up infants to assure satisfactory testing and to assure that infants with the specified diseases are detected and provided with appropriate and timely treatment.

In 1996, a Community Panel on Newborn Metabolic Screening met and recommended that five additional disorders should be screened, including congenital adrenal hyperplasia (CAH), galactosemia, hemoglobinopathies, biotinidase deficiency, and maple syrup urine disease (MSUD).

In 2002, the Newborn Metabolic Screening Advisory Committee recommended that at least 18 additional urea cycle, organic acid, fatty acid oxidation, and other amino acid disorders should be screened with the use of Tandem Mass Spectrometry (MS/MS). Tandem Mass Spectrometry is a significant new technology to detect serious and life threatening metabolic disorders in newborns. Using only one to two drops of blood, it is possible to screen for more than 30 disorders.

The Hawai'i Administrative Rules for newborn screening, Chapter 11-143, have been revised to allow for the expanded newborn screening testing panel, to contract with a single testing laboratory, and to collect newborn screening fees to be deposited in a dedicated special fund for newborn screening. The Oregon State Public Health Laboratory (OSPHL) has been awarded the competitive bid to provide the laboratory testing and tracking system.

A Coordinated Effort

Hawaii's success in screening all newborns and providing appropriate follow-up for infants with abnormal tests or confirmed disease depends on the coordinated efforts and involvement of many laboratory and health care providers. These include:

- HAWAII NEWBORN METABOLIC SCREENING PROGRAM (NBMSPP) which is responsible for statewide management of newborn screening, including program review and evaluation, follow-up and tracking of results, assessment, quality assurance, policy development, dissemination of educational brochures and manuals, continuing education, developing and monitoring of the contracts with the central newborn screening testing laboratory and mail courier service, and promulgation of Administrative Rules.
- HAWAII PRACTITIONERS AND HOSPITALS who are responsible for the collection and handling of newborn screening specimens and prompt follow-up of abnormal results and unacceptable specimens. All infants must be screened prior to hospital discharge. The primary care practitioners are responsible for providing parents with correct and current information and for prompt follow-up for abnormal screening results.
- HAWAII LABORATORIES which assist in the collection, handling, and shipping of specimens to the central newborn screening testing laboratory.
- HAWAII MEDICAL SPECIALISTS who, in conjunction with primary care providers, provide consultative and direct services regarding confirmatory testing, evaluation, treatment, and management of infants with disorders.

- CENTRAL NEWBORN SCREENING TESTING LABORATORY, which is the OREGON STATE PUBLIC HEALTH LABORATORY (OSPHL) in Portland, is responsible for testing, record keeping, quality control of laboratory testing, and notification of test results. In collaboration with the Hawai'i Newborn Metabolic Screening Program, the laboratory tracks abnormal and unresolved results. OSPHL also provides central newborn screening testing laboratory services for Oregon, Alaska, Idaho, and Nevada.
- OREGON MEDICAL CONSULTANTS who, in conjunction with the OSPHL, notify Hawai'i physicians regarding significant abnormal test results. They are available to provide consultation and information to Hawai'i physicians regarding confirmatory testing, evaluation, treatment, and management of infants with disorders.
- PUBLIC HEALTH NURSES (HAWAII STATE DEPARTMENT OF HEALTH) who, in conjunction with the Hawai'i Newborn Metabolic Screening Program, provide follow-up for the newborns delivered at home or outside of a birthing facility to ensure that the newborns are tested or that the families have been informed of the State Law regarding newborn screening. Public health nurses also provide follow-up assistance for those infants with positive screening results who have not responded to further testing.
- CHILDREN WITH SPECIAL HEALTH NEEDS BRANCH (HAWAII STATE DEPARTMENT OF HEALTH), which administers the Hawai'i Newborn Metabolic Screening Program and Children with Special Health Needs Program (CSHNP). CSHNP provides care coordination, medical nutrition therapy, and financial assistance with medical services for children diagnosed with the disorders detected through newborn screening, for families who meet the CSHNP eligibility guidelines.

Purpose of the Manual

This manual describes:

1. The disorders covered by the program, effective September 1, 2003. The disorders are described by clinical features, causes, laboratory tests, treatment, and screening practice considerations.
2. Screening practices, reporting, and follow-up. Good screening practices can greatly improve the quality of an infant's screening tests and increase the likelihood of identifying infants with disorders.
3. General program information. This includes specimen collection and mailing, reporting and follow-up of results, educational services, quality assurance, and screening forms and costs.

DISORDERS COVERED BY THE PROGRAM

Effective September 1, 2003, Hawai'i newborns are screened for the following disorders:

ENDOCRINE DISORDERS:

- Congenital adrenal hyperplasia (CAH)
- Congenital hypothyroidism

HEMOGLOBIN DISORDERS:

- Sickle cell disease and other hemoglobinopathies

METABOLIC DISORDERS:

- Biotinidase deficiency
- Galactosemia

Amino acid disorders:

- Arginase Deficiency
- Argininosuccinate lyase deficiency (ASA)
- Citrullinemia
- Homocystinuria
- Hyperphenylalanemia, including phenylketonuria
- Tyrosinemia

Organic Acid Disorders:

- Beta-ketothiolase deficiency
- Glutaric acidemia, Type 1
- Isobutyryl CoA dehydrogenase deficiency
- Isovaleric acidemia
- Malonic aciduria
- Maple syrup urine disease
- Methylmalonic acidemias (8 types)
- Propionic acidemia
- 3-Hydroxy-3-methylglutaryl (HMG) CoA lyase deficiency
- 2-Methyl-3-hydroxybutyryl CoA dehydrogenase deficiency
- 2-Methylbutyryl CoA dehydrogenase deficiency
- 3-Methylcrotonyl CoA carboxylase deficiency
- 3-Methylglutaconyl CoA hydratase deficiency
- Multiple carboxylase deficiency

Fatty Acid Oxidation Disorders:

- Carnitine uptake/transport defects
- Multiple acyl-CoA dehydrogenase deficiency (MADD)
- Short chain acyl-CoA dehydrogenase deficiency (SCAD)
- Medium chain acyl-CoA dehydrogenase deficiency (MCAD)
- Long chain 3 hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)
- Very long chain acyl-CoA dehydrogenase deficiency (VLCAD)

These are disorders which may have significant mortality and morbidity when not diagnosed presymptomatically and may not be consistently identified clinically in the neonatal period. Early detection and treatment may improve the health and development of newborns identified with these disorders.

Table I summarizes the disorders screened in Hawai'i, including the incidence, symptoms, and treatment.

Table II summarizes normal laboratory values and laboratory criteria used for follow-up. Phone follow-up (with mail confirmation) is provided for significantly abnormal test results. Mail follow-up is provided for other abnormal results.

TABLE I
SUMMARY OF DISORDERS SCREENED BY THE PROGRAM

Condition	Compound Tested for	Incidence	Symptoms if Not Treated	Treatment
Endocrine Disorders: Congenital Adrenal Hyperplasia (CAH)	17-OH Progesterone	1:12,000 1:300 in Yupik Eskimos	Addisonian Crisis in all infants; salt wasting in 2/3: dehydration, shock, hyperkalemia; virilization of females	Glucocorticoid and/or mineralocorticoid (Florinef)
Congenital Hypothyroidism	Thyroid hormones (T ₄ with TSH confirmation)	1:3,000	Mental retardation, other brain damage; growth delay	Thyroid hormone (L-Thyroxine)
Hemoglobin Disorders: Hemoglobinopathies including sickle cell anemia	Hemoglobin patterns	1:15,000 (1:400 in African Americans)	In sickle cell disease: death by sepsis or splenic sequestration anemia, sickling crises	Penicillin & comprehensive care
Metabolic Disorders: Biotinidase deficiency	Biotinidase	1:60,000	Mental retardation, seizures, skin rash, alopecia, hearing loss, death	Biotin
Galactosemia	Galactosemia enzyme (GALT)	1:60,000	Severe brain damage; liver disease; cataracts; death	Galactose-restricted diet
Amino Acids: Arginase Deficiency	Arginine	1:60,000	Irritability; developmental delay; spastic tetraplegia	Low protein diet, medication
Arginosuccinate Lyase Deficiency (ASA)	Arginine/Citrulline	1:60,000	Hyperammonemia; mental retardation; seizure; death	Low protein diet, medication
Citrullinemia	Citrulline	1:60,000	Hyperammonemia; mental retardation; seizure; death	Low protein diet, medication

TABLE I (continued)

SUMMARY OF DISORDERS SCREENED BY THE PROGRAM

Condition	Compound Tested for	Incidence	Symptoms if Not Treated	Treatment
Amino Acids (continued):				
Homocystinuria	Methionine	1:100,000	Mental retardation; dislocation of lenses; marfanoid body habitus	Pyridoxine; methionine restricted, cysteine supplemented diet
Hyperphenylalaninemia, including phenylketonuria	Phenylalanine	1:10,000	Profound mental retardation; seizures	Low phenylalanine diet
Tyrosinemia	Tyrosine	1:100,000	Vomiting, lethargy; liver disease; coagulopathy renal tubular acidosis	Medication; low phenylalanine/ low tyrosine diet
Organic Acidemias: <ul style="list-style-type: none"> • Beta-ketothiolase deficiency • Glutaric acidemia, Type I • Isobutyryl CoA dehydrogenase deficiency • Isovaleric acidemia • Malonic aciduria • Maple Syrup Urine Disease (MSUD) • Methylmalonic acidemias (8 types) • Propionic acidemia • 3-Hydroxy-3-methylglutaryl (HMG) CoA lyase deficiency • 2-Methyl-3-hydroxybutyryl CoA dehydrogenase deficiency • 2-Methylbutyryl CoA dehydrogenase deficiency • 3-Methylcrotonyl CoA carboxylase deficiency • 3-Methylglutaconyl CoA hydratase deficiency • Multiple carboxylase deficiency 	Acylcarnitines	1:53,000	Neonatal onset: irritability; lethargy; ketoacidosis; coma; death Late onset; failure to thrive; hypotonia; mental retardation Some will be asymptomatic	Dietary therapy/ Medications

TABLE I (continued)

SUMMARY OF DISORDERS SCREENED BY THE PROGRAM

Condition	Compound Tested for	Incidence	Symptoms if Not Treated	Treatment
Fatty Acid Oxidation Defects: <ul style="list-style-type: none"> • Carnitine uptake/transport defects • Multiple acyl-CoA dehydrogenase deficiency (MADD) • Short chain acyl-CoA dehydrogenase deficiency (SCAD) • Medium chain acyl-CoA dehydrogenase deficiency (MCAD) • Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD) • Very long chain acyl-CoA dehydrogenase deficiency (VLCAD) 	Acylcarnitines	1:9,300	<p>“Reyes Like” episodes; hypoketotic hypoglycemia; lethargy; cardiomyopathy; hypotonia; mental retardation; coma; death</p> <p>Mother may have had AFLP/HELLP syndrome; acute fatty liver of pregnancy</p>	Dietary therapy/ Medications

TABLE II

NORMAL VALUES AND CRITERIA FOR REQUESTING FOLLOW-UP SPECIMENS

Analyte	Normal	Phone Follow-up*	Mail Follow-up
17-OH Progesterone	≤ 35 ng/mL ≤ 10 days old, BW > 2500g ≤ 25 ng/mL > 10 days old, BW > 2500 g ≤ 60 ng/mL ≤ 10 days old, BW ≤ 2500 g ≤ 40 ng/mL > 10 days old, BW ≤ 2500 g	>70 ng/mL if ≤ 10 days, BW > 2500 g >50 ng/mL if > 10 days, BW > 2500 g >150 ng/mL if ≤ 10 days, BW ≤ 2500 g >100 ng/mL if > 10 days, BW ≤ 2500 g	>35 to ≤ 70 ng/mL if ≤ 10 days, BW > 2500 g >25 to ≤ 50 ng/mL if > 10 days, BW > 2500 g >60 to ≤ 150 ng/mL if ≤ 10 days, BW ≤ 2500 g >40 to ≤ 100 ng/mL if > 10 days, BW ≤ 2500 g
Thyroxine (T_4)	Upper 90% of T_4 determinations	T_4 in lower 10% and TSH > 100 μ IU/mL T_4 in lower 10% and TSH > 50 in > 72 hours old	T_4 in lower 3% on 2 specimens and TSH normal T_4 < 5.0 μ mg/dL, TSH normal (premature baby) T_4 in lower 10% and TSH 25 to 50 μ IU/mL if > 72 hours old and TSH 35 to 100 μ IU/mL if < 72 hours old
TSH	< 35 μ IU/mL if ≤ 72 hours old < 25 μ IU/mL if > 72 hours old or older	> 100 μ IU/mL if ≤ 72 hours old > 50 μ IU/mL if > 72 hours old	35.1–100 μ IU/mL if ≤ 72 hours old 25.1–50.0 μ IU/mL
Hemoglobin IEF	Hgb F and A	Probable homozygote	Probable homozygote
Biotinidase	Activity present	Activity absent	Partial Activity
Galactosemia Enzymes (Gal-1- PO_4 uridyl transferase, GALT)	Fluorescence present	No fluorescence and galactose ≥ 20 mg/dL or galactose < 20 mg/dL if < 48 hours old	No fluorescence and galactose, < 20 mg/dL, age ≥ 48 hours
Arginine	< 140 μ M	≥ 210 μ M	≥ 140 μ M but < 210 μ M
Citrulline	< 90 μ M	≥ 90 μ M	≥ 90 μ M with a normal 1 st specimen
Leucine	< 300 μ M	≥ 300 μ M, Leu/Ala ≥ 1.75 μ M	≥ 300 μ M, Leu/Ala < 1.75 μ M and elevation of other amino acids and on hyperalimentation (TPN)
Leucine/Alanine Ratio	< 1.75 μ M		
Methionine	< 80 μ M	≥ 120 μ M	≥ 80 μ M but < 120 μ M
Phenylalanine Phenylalanine/Tyrosine Ratio	< 200 μ M < 3.0 μ M	≥ 200 μ M, Phe/Tyr ≥ 3.0 μ M	≥ 200 μ M, Phe/Tyr < 3.0 μ M
Tyrosine	< 475 μ M	≥ 713 μ M	≥ 475 μ M but < 713 μ M

*All phoned results are followed by mailed confirmation. All of these tests are screening tests. Abnormal results need full evaluation/discussion with a consultant before a diagnosis is confirmed or treatment is started. Normal and abnormal values are subject to change based on continuing statistical evaluation.

TABLE II (continued)

NORMAL VALUES AND CRITERIA FOR REQUESTING FOLLOW-UP SPECIMENS

Analyte	Normal	Phone Follow-up*	Mail Follow-up
Organic Acidemias:			
C3 (Propionyl) Propionic acidemia, Methylmalonic acidemias (8 types), Multiple carboxylase deficiency	<10.0 µM	All abnormal results will be phoned until the significance of minor abnormalities is determined	
C3-DC (Dicarboxyl Propionyl) Malonic Aciduria	<1.9 µM		
C4 (Butyryl/Isobutyryl) Isobutyryl CoA dehydrogenase deficiency,	<1.6 µM		
C4-DC (Methylmalonyl) Methylmalonic acidemias (8 types)	<1.9 µM		
C5 (Isovaleryl/2-Methyl-butyryl) Isovaleric acidemia, 2-Methyl-3-hydroxybutyryl CoA dehydrogenase deficiency	<1.6 µM		
C5:1 (Tiglyl/3-Methylcrotonyl) 3-Methylcrotonyl CoA carboxylase deficiency (3-MCC), Beta-ketothiolase deficiency	<1.0 µM		
C5-OH (3-Hydroxyisovaleryl) 3-MCC, 3-Hydroxy-3-methylglutaryl (HMG- CoA) lyase deficiency, Malonic aciduria, Multiple carboxylase deficiency	<2.0 µM		
C5-DC (Glutaryl) Glutaric acidemia, Type I,	<1.7 µM		
C6-DC (Methylglutaryl) HMG- CoA	<3.3 µM		
Fatty Acid Oxidation Defects:			
C0 (free carnitine) Carnitine uptake/transport defects	<7.0 µM	All abnormal results will be phoned until the significance of minor abnormalities is determined	
C4 (Butyryl/Isobutyryl) SCAD Deficiency, Multiple acyl-CoA dehydrogenase deficiency (MADD)	<1.6 µM		
C5 (Isovaleryl/2-Methyl-butyryl) MADD	<1.6 µM		
C5-DC (Glutaryl) MADD	<1.7 µM		
C6 (Hexanoyl) MCAD Deficiency, MADD	<0.9 µM		
C8 (Octanoyl) MCAD Deficiency, MADD	<0.9 µM		
C10 (Decanoyl) MCAD Deficiency, MADD	<1.0 µM		
C10:1 (Decenoyl) MCAD Deficiency	<0.8 µM		
C14 (Tetradecanoyl) VLCAD Deficiency, MADD	<1.0 µM		
C14:1 (Tetradecenoyl) VLCAD Deficiency	<1.4 µM		
C16 (Palmitoyl) VLCAD Deficiency, LCHAD Deficiency, MADD	<9.7 µM		
C16-OH (Hydroxy Palmitoyl) LCHAD Deficiency	<1.1 µM		
C18 (Octadecanoyl) VLCAD Deficiency	<3.2 µM		
C18:1 (Oleyl) MADD	<6.4 µM		

*All phoned results are followed by mailed confirmation. All of these tests are screening tests. Abnormal results need full evaluation/discussion with a consultant before a diagnosis is confirmed or treatment is started. Normal and abnormal values are subject to change based on continuing statistical evaluation.

ENDOCRINE DISORDERS

CONGENITAL ADRENAL HYPERPLASIA (CAH)

Congenital adrenal hyperplasia is an inherited defect of cortisol synthesis. The adrenal gland cannot make cortisol and overproduces male hormones. Without cortisol, infants are at risk for adrenal crisis and may be unable to regulate salt and fluids, and can die. The incidence of 21-hydroxylase deficiency is 1:12,000 live births. The incidence is 1:300 in certain Yupik Eskimo populations.

Clinical Features

Unlike some other disorders in newborn screening, infants may be symptomatic at birth. By four to five months gestation, diminished cortisol production stimulates the fetal pituitary gland to produce ACTH and excessive adrenal androgens. The androgens virilize female external genitalia, but ovaries and uterus are unaffected. Male infants may have increased scrotal pigmentation or may be asymptomatic.

In two-thirds of cases, the 21-hydroxylase deficiency causes reduced production of mineralocorticoids. This leads to a hypotensive, hyperkalemic, salt-losing crisis with rapid onset of adrenocortical failure within 7-28 days of birth. This can be fatal. In one-third of cases, the infant has a “non-salt losing” or “simple virilizing form.” If untreated, children have mild postnatal virilization, rapid growth with advanced skeletal age, early puberty, and short stature as adults. In adulthood, there is hirsutism and acne. Women have irregular menses and infertility.

Causes of CAH

The term “congenital adrenal hyperplasia” or “adrenogenital syndrome” covers a group of disorders. All are due to an inborn error of steroid hormone synthesis, which blocks the production of cortisol. The low level of cortisol stimulates ACTH, causing adrenal hyperplasia

and increased secretion of steroid precursors. Different enzyme defects block the metabolic pathway at different sites and result in different clinical features. The most common disorder is 21-hydroxylase deficiency, which is the disorder tested for on newborn screening. There are variants to this disorder, which have later onset. All forms of CAH are inherited as autosomal recessive disorders.

Laboratory Tests

Screening is based on an immunoassay for a precursor steroid, 17-hydroxyprogesterone (17-OHP). Affected infants have high levels of 17-OHP. Infants with milder disorders have intermediate levels. False positives may occur in preterm, low birthweight and sick infants.

Confirmation

Confirmation is by measurement of serum 17-OHP and if salt wasting is suspected, sodium, potassium and plasma renin.

Treatment

Infants should be treated with hydrocortisone and mineralocorticoids in consultation with a pediatric endocrinologist. Infants with ambiguous genitalia need chromosome analysis to confirm gender.

Screening Practice Considerations

Female infants who are virilized or infants with ambiguous genitalia should be considered at risk for this condition, tested at birth, and monitored for electrolyte abnormalities until the diagnosis is excluded. Male infants are not usually recognized at birth. In both sexes, salt wasting and shock may develop rapidly within 7–28 days of birth. Approximately five to ten percent of infants will be detected only on a second screen. This disease kills quickly. Transport all specimens four to six hours after collection and no later than 24 hours.

RESULT	LIKELY CAUSES	ACTIONS
17-OHP >70 ng/mL, ≤10 days old, BW >2500 g 17-OHP >150 ng/mL, ≤10 days old, BW <2500 g 17-OHP >50 ng/mL, >10 days old, (any birth weight)	* CAH probable * False positive	Neonatal emergency; Oregon medical consultant contacts infant's physician by telephone and facsimile.
17-OHP >35–≤70 ng/mL, ≤10 days old, BW >2500 g 17-OHP >25–≤50 ng/mL, >10 days old, BW >2500 g 17-OHP >60–≤150 ng/mL, ≤10 days old, BW ≤2500 g 17-OHP >40–≤100 ng/mL, >10 days old, BW ≤2500 g	* Mild CAH * False positive	Oregon laboratory notifies practitioner by letter with request to repeat filter paper sample.

CONGENITAL HYPOTHYROIDISM

Congenital hypothyroidism occurs in babies who are born without the ability to produce adequate amounts of thyroid hormone. Thyroid hormone is important for normal function of all of the body's organs and is essential for normal brain development. The incidence of congenital hypothyroidism is 1:3,000. Newborn screening for congenital hypothyroidism is done in all states in our regional program.

Clinical Features

Deficiency of thyroid hormone in an infant may result in mental retardation and other signs of brain damage if it is not diagnosed and treated early in life. Many infants with congenital hypothyroidism may appear clinically normal before three months of age, by which time some brain damage has usually occurred. Only five percent of our cases were suspected by their doctor before the results of the screening were known. Laboratory test results are the only reliable means of diagnosing congenital hypothyroidism in the newborn.

When symptoms or signs are present, they may include prolonged neonatal jaundice, constipation,

lethargy and poor muscle tone, feeding problems, a large tongue, puffy face, large fontanelle, distended abdomen and umbilical hernia. Since thyroid deficiency can occur at any age, normal tests in the newborn period do not exclude deficiency in an older infant or child.

Causes of Congenital Hypothyroidism

The most common causes are total or partial failure of the thyroid gland to develop (aplasia or hypoplasia), or its development in an abnormal location (an ectopic gland). Less commonly, hypothyroidism is induced by medications (antithyroid drugs or excess iodine) in the mother, or maternal autoimmune thyroid disease with transfer of a maternal antibody which blocks the fetal thyroid development.

Laboratory Tests

The initial screening test is the T₄ (thyroxine) assay. The 10 percent of samples with the lowest T₄ results are further tested by a screening TSH assay. Different combinations of results are possible; see table below.

When the infant's physician is notified that screening results are abnormal, blood should be collected by venipuncture as soon as possible to confirm the

RESULT	LIKELY CAUSES	ACTIONS
T ₄ low/TSH elevated	<ul style="list-style-type: none"> * Hypothyroidism probable * False positive 	Lab will contact practitioner by phone and send letter requesting serum testing
T ₄ < 3.0 µg/dL, TSH pending	<ul style="list-style-type: none"> * Prematurity * Hypothyroidism possible * False positive 	Lab will contact practitioner by phone and send letter requesting further tests
T ₄ low/TSH normal (on one or two specimens unless premature)	<ul style="list-style-type: none"> * Thyroid binding globulin (TBG) deficiency * False positive * Pituitary gland problem with secondary hypothyroidism * Prematurity - see below 	Lab will contact practitioner by letter for further tests

abnormal screening results. In the case where the T4 is low and TSH is elevated, treatment can be started as soon as the serum is obtained, pending final confirmation. If the serum thyroid function tests confirm hypothyroidism, further diagnostic studies, such as a thyroid scan and bone age X-ray, may be desirable to determine the type, age of onset and severity of hypothyroidism. Generally, these studies do not change management and so are optional.

Thyroid Function in Premature Infants

In premature infants, there is a physiological reduction in blood T4 levels, TSH levels are not elevated in this situation. These cases need special observation to ensure that the low T4 levels rise into the normal range as the infant matures, but this may take several weeks.

Treatment

Treatment of congenital hypothyroidism is simple and effective. Thyroxine (e.g. Synthroid, levoxyl or levothyroid), in pill form, is crushed, mixed with milk and administered once daily. The usual starting dose is 10-15 microgram/kg of body weight daily, usually 37.5 mcg/kg to 50 mcg/kg (1 1/2-2 of 25 mcg tablets). The American Academy of Pediatrics (AAP), recommends follow-up serum T4 (or free T4) and TSH as follows:

- Initiation of treatment: two and four weeks later
- First year: every 1-2 months

- Second and third year: every two to three months
- Thereafter: every 3-12 months

Treatment goals: serum T4 in the upper 1/2 of the normal range (10-16µg/dL) and TSH normalized (<10 µIU/mL). Clinical evaluations can occur less frequently. As infants grow, the dose of thyroxine is increased. Infants should also undergo periodic developmental testing. If treatment is started early and thyroid levels are monitored closely, the development remains normal.

Screening Practice Considerations

Hypothyroidism is the most common disorder covered by the program. Ninety percent of hypothyroid infants are detected on the first specimen even if it is collected a few hours after birth. In 10 percent of cases, hypothyroidism only develops in the weeks after birth and is detected on a second screening test as production of thyroid hormone dwindles after birth. **Practitioners therefore must remain alert to clinical symptoms in older infants despite normal initial screening.**

False positive results may occur if the specimen is collected with the first few hours after birth, as the TSH rises in response to the extrauterine environment. Topical iodine may cause transient hypothyroidism in prematures.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

HEMOGLOBIN DISORDERS

SICKLE CELL DISEASE AND OTHER HEMOGLOBINOPATHIES

The primary goal of hemoglobinopathy screening is diagnosis of significant sickling hemoglobinopathies in the neonatal period, before symptoms occur. Newborn diagnosis of sickle cell disease, if coupled with family education and centralized comprehensive care, can markedly lower morbidity and mortality.

Homozygous sickle cell disease (SCD) occurs when the recessive gene for hemoglobin S, sickle hemoglobin, is inherited from both parents. The term “clinically significant sickling syndrome” also includes conditions resulting from inheritance of one gene for hemoglobin S and certain other unusual hemoglobins, such as beta thalassemia or hemoglobin C. These doubly heterozygous conditions tend to be less severe than SCD, though all are capable of producing severe complications. The incidence of SCD in the African American population is 1:400, but also occurs at a lower frequency among all other ethnic groups. The disease incidence in a population depends on the population’s ethnic composition.

Clinical Features

Sickle syndromes are systemic diseases and may involve any organ. They are characterized clinically by chronic hemolysis, intermittent vaso-occlusion and marked variability. Some patients experience unremitting complications, others lead a full and productive life. Early manifestations are often life-threatening and include overwhelming infection due to splenic dys-

function, splenic sequestration crisis, and aplastic crisis with profound anemia. Prior to newborn diagnosis and preventive care, mortality in the United States was 8-30 percent in the first three years of life. Some important complications include vaso-occlusive pain syndromes, osteomyelitis, acute chest syndrome, stroke, priapism, pyelonephritis, gallstones, skin ulcers, retinopathy, and decreased life expectancy.

Other significant hemoglobinopathies are less common and even more variable. Their manifestations range from very mild chronic hemolysis to severe dyserythropoiesis requiring a lifetime of transfusion support. Early detection of these, however, may prevent unnecessary diagnostic and therapeutic intervention.

Laboratory Tests

Screening for sickle cell disease is done using dried blood spots submitted for newborn screening tests. All first filter paper samples are screened for hemoglobinopathies using isoelectric focusing (IEF). Various hemoglobin patterns occur. If an abnormality is detected, the sample is reanalyzed using high performance liquid chromatography (HPLC). If a hemoglobin abnormality is detected on the first filter paper sample, the second filter paper sample is also analyzed by IEF and HPLC. Thus, each hemoglobin abnormality is verified four times, using two different techniques on two different samples. Solubility tests (Sickle-dex, Sickle-prep, etc.) are never appropriate in infancy and should not be used to confirm screening results.

RESULTS	LIKELY CAUSE	ACTION
FS (absence of A)	* Sickle cell disease or Sickle beta thalassemia	Lab will report to follow-up team who contacts practitioner by phone with instructions for diagnosis and treatment
FSC (absence of A)	* Sickle hemoglobin SC disease	Lab will report to follow-up team who contacts practitioner by phone with instructions for diagnosis and treatment
FC (absence of A)	* Homozygous C disease	Lab will report to follow-up team who contacts practitioner by phone with instructions for diagnosis and treatment
FE (absence of A)	* Homozygous hemoglobin E or hemoglobin E-beta thalassemia	Lab will report to follow-up team who contacts practitioner by phone with instructions for diagnosis and treatment
FAS	* Sickle cell carrier * Sickle beta thalassemia * Sickle cell disease in transfused infant	Lab will report by letter regarding test results and any other recommendations
FAC	* Hemoglobin C carrier * Homozygous C disease in a transfused infant	Lab will report by letter regarding test results and any other recommendations
FA+slow band	* Possible carrier for hemoglobin E, O, D, or G	Lab will report by letter regarding test results and any other recommendations
FA+fast band	* Possible alpha thalassemia * Bart's hemoglobin is a marker for alpha thalassemia	Lab will report by letter regarding test results and any other recommendations
F only	* Premature infant * Beta thalassemia major	Lab will report by letter regarding test results and any other recommendations
Predominance of A	* Transfused infant * Patient outside of neonatal age range	Lab will report by letter regarding test results and any other recommendations

Treatment

Infants with significant hemoglobinopathies should have a primary care provider and receive periodic evaluation in a comprehensive care setting. Therapy begins with education of care-givers and includes prophylactic penicillin, prompt evaluation and empirical treatment of any febrile illness, and immunizations including those for encapsulated bacteria. Close

attention is necessary for the common problems of poor growth, recurrent pain and febrile illnesses. Organ-specific complications, sedation and general anesthesia require special attention. Other treatments, including the use of blood products and investigational therapies depend on clinical course.

Carrier Detection Makes Hemoglobin Screening Different

This is the only newborn screening test which regularly identifies carriers (heterozygotes) as well as those affected by a given disease. In fact, many more carriers than disease states are identified for all hemoglobinopathies. If both parents are carriers of an autosomal recessive genetic trait, the risk of any infant of that couple being homozygous is 1/4. While the best way to handle this genetic information has yet to be agreed upon, several principles are currently operative: 1) The family is entitled to the information and it is private. 2) If both parents of a SCD carrier infant are African American, they have at least a 1/50 risk of having a subsequent child with SCD, because at least one of them is now known to be a carrier. The family should be offered testing and genetic counseling. If the family declines participation, this should be documented. 3) The abnormal screening results may

need to be confirmed, using a liquid blood specimen. The Medical Consultant for hemoglobinopathy screening is available for assistance.

Screening Practice Considerations

Newborn screening for hemoglobinopathies is not done on the second specimen unless an abnormality has been identified on the first specimen. It is crucial to use the first kit for the first test; the cards are not interchangeable. Transfusion of red blood cells prior to drawing the newborn screening specimen will invalidate the hemoglobinopathy test. **Obtain a specimen before any transfusion.** Some hemoglobinopathies, particularly the thalassemias, are not reliably detected through newborn screening and a normal screening result does not eliminate the possibility that a patient has a hemoglobinopathy. Further testing or consultation should be sought if indicated by clinical suspicion.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

METABOLIC DISORDERS

BIOTINIDASE DEFICIENCY

Detection of biotinidase deficiency requires urgent follow-up. This recessively inherited disorder affects the regeneration of the vitamin-cofactor biotin and impairs the metabolism of mitochondrial carboxylases. The incidence is estimated at 1:60,000 births. Screening for biotinidase deficiency is performed in all the states in our regional program.

Clinical Features

Infants with biotinidase deficiency are normal at birth, but develop one or more of the following

symptoms after the first weeks or months of life: hypotonia, ataxia, seizures, developmental delay, alopecia, seborrheic dermatitis, hearing loss and optic nerve atrophy. Metabolic acidosis can result in coma and death.

Laboratory Tests

Detection of enzyme activity is by a qualitative colorimetric assay. In the presence of the enzyme a color change occurs.

RESULTS	LIKELY CAUSES	ACTIONS
Color change does not occur	<ul style="list-style-type: none"> * Biotinidase deficiency possible * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.

Treatment

Daily biotin supplements clear the skin rash and alopecia and improve the neurological status in patients not diagnosed by screening. With early diagnosis and treatment made possible by screening, all symptoms can be prevented.

Screening Practice Considerations

The enzyme is prone to damage if the sample is delayed in the mail or exposed to high temperatures. Transfusion of red cells prior to drawing the newborn screening specimen will invalidate the biotinidase assay. **Obtain a specimen before transfusion.**

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

GALACTOSEMIA

Detection of galactosemia requires urgent follow-up and should be considered a potential medical emergency. Dietary galactose is most commonly ingested as lactose, the principle carbohydrate of human milk and most non-soy commercial infant formulas; it is hydrolyzed to glucose and galactose in the intestine. After absorption it is metabolized by several enzymes including galactokinase and galactose-1-phosphate uridyl transferase (GALT). When deficient, the latter causes galactosemia (1:60,000 births). Galactosemia is a recessively inherited condition and screening is performed in all the states in our regional program.

Clinical Features

The early clinical features of severe untreated galactosemia include neonatal hypoglycemia, liver damage, jaundice, failure to thrive, lethargy and sepsis. Vitreous hemorrhage has been reported in some infants. Death may result from gram-negative sepsis within one to two weeks of birth. If the infant

is untreated and survives the neonatal period, cataracts, cirrhosis, renal Fanconi syndrome and mental retardation are usual.

There are several genetic variants with less severe reduction in the enzyme activity (e.g., the Duarte variant). Most of these cases are asymptomatic and are detected on newborn screening because of abnormalities. Recommendations for confirmatory testing are made by the medical consultants. The need for treatment of Duarte variant galactosemia is controversial and the consultants are available for consultation. The screening test is not designed to detect Duarte variant galactosemia and is not completely sensitive for this purpose.

Laboratory Tests

Two screening tests are used to detect galactosemia in a two tiered sequence (see diagram):

- (1) GALT activity (Beutler Test) :

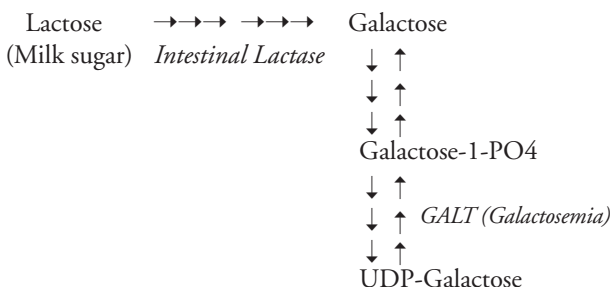
The enzyme test depends upon fluorescence produced by the normal galactose enzyme cascade in red blood cells. A temporarily abnormal result (diminished or absent fluorescence) is found in 1:2,000 infants. The test

RESULTS		LIKELY CAUSES	ACTIONS
GALT Test	Galactose Metabolites		
Abnormal	≥ 20 mg/dL	<ul style="list-style-type: none"> * Severe galactosemia * Variant galactosemia * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.
Abnormal	< 20 mg/dL	<ul style="list-style-type: none"> * Severe galactosemic with little lactose intake * Variant galactosemia * Other enzyme defects in red blood cells * Improperly handled sample (heat damage or transit delay) 	Contact by letter if > 48 hrs old; contact by phone if < 48 hrs old or if not on lactose

may be persistently abnormal if the enzyme activity is <50% of normal. It does not differentiate milder variants from severe defects. All infants are screened with the Beutler test.

(2) Galactose (Hill Test):

Slight elevations (up to 20 mg/dL) can occur in normal neonates, but galactose metabolites are greatly elevated in infants with galactosemia if they are receiving a lactose-containing formula or breast milk. The Hill test is a fluorometric chemical spot test which measures galactose and galactose-1-phosphate. Liver disease may also cause an elevation of galactose metabolites. Only infants with an abnormal Beutler or who have been transfused will be screened with the Hill Test.



Treatment

Galactosemia is treated by dietary galactose restriction. This diet must be followed for life and requires close supervision. Even with early diagnosis and strict dietary restrictions children with galactosemia are at risk for speech disorders, growth and developmental delays and in females, ovarian failure.

Screening Practice Considerations

The GALT test should be abnormal in virtually all severe classic galactosemic infants even if the specimen is obtained before lactose is ingested, unless the infant has been transfused. **Obtain a specimen before any transfusion.** The GALT test is prone to inaccuracy if the sample is delayed in the mail or exposed to high temperature or humidity.

Galactose accumulation depends on **lactose** ingestion so that blood galactose metabolites may be normal in infants receiving soy based formula. This disease kills quickly. Transport all specimens four to six hours after collection and no later than 24 hours after collection.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

AMINO ACID DISORDERS

UREA CYCLE DISORDERS *

The urea cycle is the metabolic pathway responsible for the detoxification of ammonia and for the synthesis of arginine and urea. There are six enzymes in the urea cycle, each of which if missing, will result in hyperammonemia. Six disorders, each with genetic and clinical variability have been reported, each representing one of the enzymes of the urea cycle. Three of these disorders can be detected in newborn screening tests*:

1. Arginase deficiency
2. Argininosuccinic aciduria
3. Citrullinemia

Estimated incidence of these conditions is 1:60,000. They are inherited as autosomal recessive traits.

Arginase Deficiency

Clinical Features

Arginase deficiency is associated with irritability, unconsolable crying, anorexia, vomiting and developmental delay in infancy. This progresses to spastic tetraplegia with lower limbs more severely affected than the upper, psychomotor retardation, hyperactivity and growth failure. Hyperammonemia may result in encephalopathy, but is often milder than that seen in other urea cycle defects.

Citrullinemia & Argininosuccinic Aciduria

Clinical Features-Neonatal Onset

Infants with severe citrullinemia and argininosuccinic aciduria appear normal at birth and for the first 24 hours. Usually between 24-72 hours symptoms of hyperammonemia will appear as lethargy, vomiting, hypothermia, hyperventilation progressing to coma, cerebral edema and death without intervention. Unfortunately, a misdiagnosis of sepsis is made in 50% of the cases, wasting precious time. In addition to ammonia, glutamate/ glutamine are usually elevated. Specific elevations in citrulline, argininosuccinic acid, arginine, and orotic acid are helpful in determining the type of urea cycle defect.

Clinical Features-Late Onset

Late onset forms of urea cycle defects most often present as non-specific developmental delay, seizures or other neurological symptoms which are associated with a history of repeated bouts of lethargy, vomiting, irritability or headaches. Food refusal and failure to thrive are not uncommon.

Laboratory Tests

Elevations of citrulline and arginine are detected by MS/MS. The laboratory cutoff for citrulline is $<90 \mu\text{M}$; for arginine $<140 \mu\text{M}$. Argininosuccinic acid cannot be distinguished from citrulline using tandem mass spectrometry. Transient elevations of plasma arginine and citrulline in the newborn are unusual unless the infant is premature and/or receiving hyperalimentation.

** Screening will NOT identify all urea cycle disorders and sensitivity and specificity for Arginase deficiency is unknown. Practitioners should remain alert to the possibility of hyperammonemia in any infant with lethargy and coma in the first few days of life.*

RESULTS	LIKELY CAUSES	ACTIONS
Arginine >210 μ M	<ul style="list-style-type: none"> * Arginase deficiency possible * Transient argininemia * Liver disease * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.
Citrulline \geq 90 μ M	<ul style="list-style-type: none"> * Citrullinemia, argininosuccinic aciduria possible * Transient citrullinemia * Liver disease * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.
Citrulline \geq 90 μ M on second specimen	<ul style="list-style-type: none"> * Mild citrullinemia, argininosuccinic aciduria possible * Transient citrullinemia * Liver disease * False positive 	Lab requests repeat filter paper specimen

Treatment

All patients with a neonatal presentation represent medical emergencies and outcomes may be variable. Patients with neonatal onset disease will typically require aggressive treatment with hemodialysis. All patients, both late onset and those rescued from neonatal hyperammonemia, will require treatment with low protein diets and medications to prevent hyperammonemia and remove toxic compounds. The outcome for patients rescued from prolonged neonatal hyperammonemia is dismal. Brain damage is likely. Even patients treated prospectively from birth may not be normal. Those with late onset

disease fare better, and presymptomatic diagnosis and treatment may allow normal development.

Screening Practice Considerations

Infants with neonatal onset disease may be sick or die before screening results are known. Collect specimens before discharge and transport within four to six hours of collection and no longer than 24 hours after collection. Practitioners must remain alert to the possibility of these disorders in any newborn with lethargy or coma.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

HYPERMETHIONINEMIA

Homocystinuria (cystathionine beta-synthase deficiency) *

The most common form of genetic homocystinuria is cystathionine beta-synthase deficiency (CBS). CBS is required for conversion of methionine to cysteine and deficiency results in the accumulation of homocystine, methionine and cysteine-homocystine disulfides in the blood and urine. Unfortunately, methionine rises slowly in affected infants and may not be detectable on specimens obtained in the first few days after birth. Homocystinuria is inherited as an autosomal recessive trait. Occurs in approximately 1:100,000 births.

Clinical Features

Untreated patients appear normal at birth, but by the first or second year mental retardation may be apparent, most will develop dislocation of the lenses and a marfanoid body habitus, osteoporosis, and

ultimately thromboembolism may develop which can result in serious and permanent disabilities or death.

Methionine Adenosyltransferase (MAT) Deficiency

Approximately 20 infants in the U.S., identified through newborn screening with persistently elevated methionine have been shown to have MAT deficiency. All but two patients have been asymptomatic, with normal growth and development. Two patients have had demyelination of the brain, but it is not clear that this is a result of MAT deficiency or other causes.

Laboratory Test

Elevation of methionine is detected by MS/MS; normal methionine levels are $<80 \mu\text{M}$. Transient elevations of plasma methionine in the newborn is unusual unless the infant is premature and/or receiving IV amino acid preparations. (i.e., TPN, hyperalimentation).

** Not all forms of homocystinuria or even all cases of CBS deficiency will be detected by MS/MS.*

RESULTS	LIKELY CAUSES	ACTIONS
Methionine $\geq 80 - 120 \mu\text{M}$	<ul style="list-style-type: none"> * Homocystinuria/MAT deficiency possible * Tyrosinemia, Type 1 * Liver disease * Hyperalimentation * High protein diet * False positive 	Lab requests repeat filter paper specimen by mail
Methionine $\geq 120 \mu\text{M}$	<ul style="list-style-type: none"> * Homocystinuria/MAT deficiency probable * Tyrosinemia, Type 1 * Liver disease * Hyperalimentation * High protein diet * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.

Treatment

Some patients will respond to pyridoxine in large doses (250-1200 mg/day). For patients unresponsive or partially responsive to pyridoxine, a methionine restricted, cysteine supplemented diet is usually effective. Betaine is usually effective. The outcome for treated patients is dependent on the age at diagnosis, adherence with therapy and severity of defect.

Screening Practice Considerations

Methionine rises slowly in affected infants, so that the first screening specimen may be normal; 80% of the homocystinuria patients detected in the NWRNBSP have been found on routine second tests.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

PHENYLKETONURIA (PKU) & HYPERPHENYLALANINEMIA

Detection of elevated phenylalanine levels requires urgent follow-up. This disorder is due to a recessively inherited enzyme defect in which the body cannot use the amino acid phenylalanine properly. All other metabolic processes are intact, but phenylalanine, which comes from all dietary protein, accumulates in the blood to toxic levels. Screening for PKU is performed in all states in our regional program.

Clinical Features

Infants with PKU seem to be normal for many months, however, without treatment, severe mental retardation, eczema and other problems usually develop. In older untreated patients the skin and hair may be fair, the eyes may be blue and a mousey odor of the skin or urine is common. Untreated blood phenylalanine level is often over 1200 μM .

Overall, PKU occurs in about 1 in 10,000-15,000 Caucasian and Hispanic births. It is less common in other races, but the racial frequency distribution is not well known. Although severe mental deficiency is the rule in untreated cases, occasional asymptomatic adults are found with normal or near normal intelligence, despite high phenylalanine levels.

Plasma phenylalanine is not detectably elevated in cord blood. It starts rising within 24 hours after birth and often reaches 1200 μM or more within a few days. The screening test is often abnormal within 24 hours and almost uniformly abnormal within 48 hours of birth.

Variant Forms of PKU (Hyperphenylalaninemia)

There are several intermediate forms of hyperphenylalaninemia in which the plasma phenylalanine

levels are lower than in classic PKU (180-1200 μM). In these cases, mental retardation is variable and, in the milder variants, is completely absent. In infancy, these patients can mimic severe PKU, and for adult women the risk of the maternal PKU syndrome increases in proportion to the plasma phenylalanine.

Some forms of hyperphenylalaninemia are caused by defects of bipterin metabolism and blood phenylalanine levels are variable. These patients have progressive neurological damage with seizures and steady deterioration which becomes noticeable sometime between 6 and 20 months of age despite early treatment with a low phenylalanine diet. Definitive tests can differentiate these variant forms of PKU. In view of the severity of this group of diseases, all infants with persistently abnormal levels of phenylalanine will be recommended to have testing by special blood and urine tests for bipterin abnormalities. Information regarding this testing is provided through the metabolic consultants.

Maternal PKU and Hyperphenylalaninemia

Women with significant hyperphenylalaninemia have an increased risk of miscarriage and their offspring (who usually do not have PKU) may have intra-uterine growth retardation which persists postnatally. More than 90 percent of infants of untreated mothers with classical PKU have microcephaly, mental retardation, and/or congenital heart defects. They have a transient elevation of phenylalanine (240-1200 μM) which falls to normal within 24 hours. A screening test on the **mothers** of infants with transient hyperphenylalaninemia, particularly if the infant's sample was collected in the first 24 hours after birth is recommended. Phenylalanine restricted diet begun prior to conception and during pregnancy can often prevent damage to the fetus.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

Laboratory Tests

PKU and hyperphenylalaninemia are detected using tandem mass spectrometry (MS/MS); the normal phenylalanine level is $< 200 \mu\text{M}$.

Treatment

With proper treatment, mental retardation is totally preventable. Treatment should be started as soon after birth as possible (certainly before 3 weeks of age) in any infant recommended for treatment by the consultants and should be continued indefinitely. Frequent monitoring is required, especially in the first weeks, because variant forms of hyperphenylalaninemia may be indistinguishable from true PKU and improper nutritional therapy can be fatal.

If treatment is not started for some weeks, the results are more variable and the I.Q. tends to be lower. Patients whose treatment begins after six months are likely to remain mentally retarded. Older

patients usually show little change in I.Q. with treatment, but a low phenylalanine diet may help to control serious behavior problems.

Screening Practice Considerations

Detection may depend on the amount of protein ingested or endogenously produced by the infant, but most affected babies (90 percent) have abnormal results even in the first 24 hours of life regardless of intake. Those with milder forms of hyperphenylalaninemia require longer periods of feeding or catabolism to develop abnormal tests.

If an infant is tested < 24 hours of age, a repeat test must be done at or after ≥ 24 hours but before 14 days of age.

Contamination of the filter paper with food, or liquids containing NutraSweet (Aspartame) may cause false positive results or inadequate specimen.

RESULTS	LIKELY CAUSES	ACTIONS
Phenylalanine $\geq 200 \mu\text{M}$, Phe/Tyr $\geq 3.0 \mu\text{M}$	<ul style="list-style-type: none"> * PKU possible * Variants forms of PKU * Mother has PKU * False positive * Transient hyperphenylalaninemia 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

TYROSINEMIA

Elevated tyrosine may result from several inherited defects of tyrosine catabolism, delayed maturation of enzymes or liver disease.

Transient Tyrosinemia

Transient tyrosinemia of the newborn is common (1:1,000) and more common among Inuit and Eskimo populations in Alaska. Transient tyrosinemia is thought to arise from delayed maturation of the liver enzyme, 4-hydroxyphenylpyruvic acid dehydrogenase (4HPPD), coupled with increased protein intake and/or occult ascorbic acid deficiency. Tyrosine levels may be quite high ($>500 \mu\text{M}$) peaking at 14 days of life and resolved by one month. Premature infants may have prolonged hypertyrosinemia.

Clinical Features

Transient tyrosinemia of the newborn may present with lethargy or decreased motor activity, but is usually a biochemical abnormality found in an otherwise normal newborn. For normal newborns transient tyrosinemia is not associated with long term sequela, although this has not been systematically studied.

Treatment

Transient tyrosinemia, while probably benign, may in some cases be treated with protein restriction to 2g/kg/day and administration of ascorbic acid (50-200 mg/day orally for 1-2 weeks) to infants found to have elevated tyrosine. If the infant is breast feeding, ascorbic acid alone may be administered.

Hepatorenal Tyrosinemia

Tyrosinemia, Type I or fumarylacetoacetate hydrolase (FAH) deficiency occurs in 1:100,000 births. Hepatorenal tyrosinemia is inherited as an autosomal recessive trait.

Clinical Features

Tyrosinemia, Type I causes severe liver and renal disease and peripheral nerve damage. Presentation in infancy includes vomiting, lethargy, diarrhea and

failure to thrive. Liver disease with hepatomegaly, hypoproteinemia, hyperbilirubinemia, hypoglycemia and coagulopathy may be present. In an international survey of 108 patients, 13% (n=14) became symptomatic in the first two weeks of life and 36% (n=39) in the first two months. Renal proximal tubular dysfunction results in aminoaciduria, hyperphosphaturia and hypophosphotemic rickets. Untreated, death in infancy or childhood from acute liver failure, neurological crises, or hepatocellular carcinoma is usual.

Treatment

Therapy with NTBC [2-(nitro-4-trifluoromethylbenzoyl)-1-3-cyclohexanedione] blocks the formation of the toxic metabolites. NTBC is effective in preventing or halting liver and renal damage and averting acute neurological crises. Long term outcome of NTBC therapy on the development of hepatic carcinoma is yet unknown. Liver transplantation may be used in selected cases. Adjunct therapy with dietary restriction of phenylalanine and tyrosine as well as symptomatic treatment of clotting defects, rickets and proximal tubular losses may also be indicated.

Occulocutaneous Tyrosinemia

Tyrosinemia, Type II is caused by a deficiency of the enzyme tyrosine aminotransferase (TAT) and is inherited as an autosomal recessive trait. TAT deficiency is rare, with about 50 cases described worldwide.

Clinical Features

TAT is manifested primarily in the eyes, the skin and the central nervous system. In the eyes, tyrosine crystals accumulate, resulting in painful corneal erosions. Equally painful hyperkeratotic plaques develop on the plantar surfaces of hands, feet and digits. Symptoms usually develop in the first year of life, but have been present on the first day of life or not occur until adulthood. A variable degree of mental retardation is present in about 50% of cases.

Treatment

A diet restricting phenylalanine and tyrosine is effective in clearing and/or preventing ulcerations.

Laboratory Tests

Tyrosinemia is detected using MS/MS; the cutoff tyrosine level is $<475 \mu\text{M}$. There is considerable overlap in tyrosine levels between normal infants, those with transient tyrosinemia and affected infants, making the tyrosine level itself not very specific.

Clinical correlation, blood amino acids and urine succinylacetone are necessary to differentiate these cases.

Screening Practice Considerations

Tyrosine may be **slow to rise** in affected infants, making it more likely to be found on routine second testing. Practitioners must remain alert to the possibility of tyrosinemia in any infant with liver disease, corneal or keratotic lesions.

RESULTS	LIKELY CAUSES	ACTIONS
Tyrosine $\geq 475 \mu\text{M}$	<ul style="list-style-type: none">* Transient Tyrosinemia* Tyrosinemia possible* Liver disease* Hyperalimentation* False Positive	Lab phones results to consultants, who phone practitioner with follow up recommendations. Notification is followed up by mail.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

ORGANIC ACIDEMIAS

Organic acidemias (OA) result from enzyme deficiencies involved in the catabolism of multiple amino acids and other metabolites. Maple syrup urine disease is detected by an elevation of the amino acid leucine and an abnormal leucine/alanine ratio. All the other OAs are detected through elevations in acylcarnitines. All have autosomal recessive inheritance and collectively have an incidence of 1:53,000. The following OAs are screened for by MS/MS:

- Beta-ketothiolase deficiency
- Glutaric acidemia, Type 1 (glutaryl-CoA dehydrogenase deficiency)
- Isobutyryl CoA dehydrogenase deficiency
- Isovaleric acidemia, (isovaleryl-CoA dehydrogenase deficiency)
- Malonic aciduria
- Maple Syrup Urine Disease (branched chain alpha-ketoacid dehydrogenase deficiency)
- Methylmalonic acidemias, methylmalonyl CoA mutase deficiency and 5 defects of B12 metabolism
- Propionic acidemia
- 3-Hydroxy-3-methylglutaryl (HMG) CoA lyase deficiency
- 2-Methyl-3-hydroxybutyryl CoA dehydrogenase deficiency
- 2-Methylbutyryl CoA dehydrogenase deficiency (mitochondrial acetoacetyl-CoA thiolase deficiency)
- 3-Methylcrotonyl CoA carboxylase (3MCC) deficiency
- 3-Methylglutaconyl CoA hydratase deficiency (3-methyl-glutaconic aciduria, Type 1)
- Multiple carboxylase deficiency

Clinical Features

Neonatal Onset: Most of these disorders have severe forms that present in the first week of life and constitute a neonatal emergency. Infants are generally well at birth, but develop poor feeding, irritability, lethargy, vomiting, and severe metabolic ketoacidosis, with or without hypoglycemia, in the first few days of life; this progresses to coma and death in the first

month if treatment is not instituted. In methylmalonic and propionic acidemias, ammonia may also be elevated. Isovaleric acidemia is also associated with the odor of “sweaty socks.” Maple Syrup Urine Disease has a characteristic “burnt sugar” or “maple syrup” odor which can be noticed in the urine, sweat and ear cerumen of the affected infant as early as the fifth day of life. Isobutyryl CoA dehydrogenase deficiency is associated with a dilated cardiomyopathy. Even with prompt treatment, many infants with neonatal forms of organic acidemias sustain psychomotor damage and may have significant long term morbidity. These infants may be ill before the results of the screening tests are known.

Late Onset: Milder variants may present with an acute decompensation brought on by an intercurrent illness similar to those described above, or with failure to thrive, hypotonia mental retardation and a history of bouts of vomiting, protein intolerance, acidosis and/or hypoglycemia. While these patients typically have ‘milder’ disease, the neurological damage may be just as severe as those presenting earlier. Newborn screening may be very beneficial to these infants as the initial crisis may be prevented.

Asymptomatic Cases: There are numerous reports of cases of isolated 3-methylcrotonyl-CoA carboxylase deficiency who have remained asymptomatic despite biochemical and/or enzymatic confirmation of the condition. The etiology of these variant presentations is not yet understood.

Glutaric Acidemia, Type 1: Glutaric acidemia, Type 1 or GA1 is an organic acidemia with clinical features unlike those described above. In this disease, there is an accumulation of glutaric acid and 3-hydroxy glutaric acid, which are believed to be toxic to cells, particularly in the central nervous system. The classic presentation is macrocephaly at or shortly after birth. Infants have a period of apparently normal development but may have soft neurological signs, like jitteriness, irritability and truncal hypotonia. Generally between 6 and 18 months of age, patients will experience an acute encephalopathic episode resulting in damage to the basal ganglia and

atrophy of the caudate and putamen. Severe dystonia, dyskinesia and other neurological findings result, either in a static or slowly progressive form. These children are often misdiagnosed as having extrapyramidal cerebral palsy. Approximately 25% of GA1 patients will present with motor delay, hypotonia, dystonia and dyskinesia that develop gradually during the first few years of life, without any apparent acute crisis. Intellect is relatively intact. Infants with GA1 are prone to acute subdural and retinal hemorrhages, after minor head trauma. This can be misdiagnosed as child

abuse. Finally, five percent of all Amish patients have been completely asymptomatic without any crises and normal development. Neurological crises and symptoms rarely occur after five years of age.

Laboratory Tests

All these disorders are detected by MS/MS. Leucine can be elevated in infants receiving hyperalimentation, usually along with other amino acid elevations. In a normal newborn, however, elevations of these compounds are unusual and require rapid follow up.

RESULT	LIKELY CAUSES	ACTIONS
Leucine > 300 μ M Leu/ala >1.75	<ul style="list-style-type: none"> * MSUD possible * Hyperalimentation * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.
C3 (Propionyl) >10.0 μ M	<ul style="list-style-type: none"> * Methylmalonic acidemias possible * Multiple carboxylase deficiency possible * Propionic acidemia possible * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.
C3 (DC Malonyl) >1.9 μ M	<ul style="list-style-type: none"> * Malonic aciduria possible * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.
C4 (Butyryl) >2.3 μ M	<ul style="list-style-type: none"> * Isobutyryl CoA dehydrogenase deficiency possible * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.
C4-DC (Methylmalonyl) >1.6 μ M	<ul style="list-style-type: none"> * Methylmalonic acidemias possible * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.
C5 (Isovaleryl) >1.0 μ M	<ul style="list-style-type: none"> * Isovaleric acidemia possible * 2-Methylbutyryl CoA dehydrogenase deficiency possible * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.
C5-DC (Glutaryl) >1.7 μ M	<ul style="list-style-type: none"> * Glutaric acidemia, Type 1 possible * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.

(table continued on next page)

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RESULT	LIKELY CAUSES	ACTIONS
C5-OH (Methylcrotonyl) >1.7 μ M	<ul style="list-style-type: none"> * 2-Methyl-3-hydroxy butyryl CoA dehydrogenase deficiency possible * 3-Methylcrotonyl CoA carboxylase deficiency possible * 3-Methylglutaconyl CoA hydratase deficiency possible * Multiple carboxylase deficiency possible * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.
C5:1 (Tiglyl/3-methylcrotonyl) >2.0 μ M	<ul style="list-style-type: none"> * Beta ketothiolase deficiency possible * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.
C5-OH, C6-OH/DC Multiple elevations	<ul style="list-style-type: none"> * 3-Hydroxy-3-methyl glutaric aciduria possible * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.
C6-DC (Glutaryl) > 1.0 μ M	<ul style="list-style-type: none"> * 3-HMG CoA lyase deficiency possible * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.

Treatment

Any baby in whom a neonatal onset organic acidemia is suspected should be treated as a neonatal emergency. Infants with these disorders should in most, if not all, cases be transferred to a major medical center as quickly as possible. The investigations and management are very complicated. Death or permanent neurological deficits can occur rapidly in untreated cases. Infants who are asymptomatic at the time that abnormal screening results are reported may be handled less urgently, depending on the clinical status and individual circumstances. Treatments, which must be continued for life, consist of strict dietary amino acid restrictions and medications.

Infants with GA1, in addition to diet and medications, must have aggressive supportive care during intercurrent illness through out the first 5-6 years of life.

This generally entails hospitalization, IV fluid and calories during all febrile or flu like illnesses.

For individuals with MSUD, isovaleric acidemia and one or two other organic acidemias, prospective and early identification through newborn screening will be life saving and outcomes are expected to be good. For others, including those with GA1, the outcomes are less sure at this time.

Screening Practice Considerations

Affected infants must be detected early if major problems are to be prevented. Collect specimens before discharge and transport within four to six hours of collection and no later than 24 hours after collection. Practitioners must remain alert to the possibility of these diseases in any infant with lethargy, acidosis or coma.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

FATTY ACID OXIDATION (FAO) DISORDERS

Mitochondrial beta-oxidation of fatty acids is crucially important in the body's ability to produce energy, particularly during fasting. In infants, a "fasting" state can be produced in as little as 4 hours. Fatty acids must be transported into the cytoplasm and then into the mitochondria for oxidation; carnitine is required for these transport steps. Once in the mitochondria, fatty acid chains 4-18 carbons in length must be oxidized, 2 carbons at a time, each reaction using a chain-specific enzyme, before ketogenesis can occur. There are over 20 individual steps in beta-oxidation some with multiple enzyme complexes. An enzyme block anywhere in this process or a carnitine deficiency will result in hypoketotic hypoglycemia and tissue damage related to the toxic accumulation of unoxidized fatty acids. At least 16 separate enzyme disorders have been identified, many of which may be identified by MS/MS by measuring the accumulation of various acylcarnitines.

Fatty acid oxidation disorders*

- Carnitine transport defect (enzyme unknown)
- Carnitine/acylcarnitine translocase (CT) deficiency
- Carnitine palmitoyl transferase (CPTI) deficiency
- Carnitine palmitoyl transferase II (CPTII) deficiency
- Very long chain acyl-CoA dehydrogenase (VLCAD) deficiency
- Long chain L-3 hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency
- Medium chain acyl-CoA dehydrogenase (MCAD) deficiency
- Short chain acyl-CoA dehydrogenase (SCAD) deficiency
- Multiple acyl-CoA dehydrogenase deficiency (MADD aka GA 2)
- Trifunctional protein (TFP) deficiency

MCAD is the most common, approximately 1:10,000 births; LCHAD is less frequent, but not rare. The true incidence of the other disorders is unknown. All are inherited as autosomal recessive traits.

Clinical Features

FAO disorders have overlapping symptoms and organ involvement. They fall into three major categories as described below.

Hepatic: There is no typical age of presentation, which may be on the first day of life through adulthood. Precipitating factors are fasting and/or stress associated with intercurrent illness. Patients present with "Reyes-like" symptoms including vomiting, lethargy, hypoketotic hypoglycemia, mild hyperammonemia, hyperuricemia, hypocarnitinemia and abnormal liver function tests. Liver biopsy often shows steatosis. Hepatic presentation is common in MCAD, VLCAD, LCHAD, neonatal CPT I & II and mild CT deficiency. Approximately 25 percent of individuals with MCAD will die during their first episode. In survivors, about 20 percent sustain significant neurological damage, presumably due to hypoglycemia. Patients with LCHAD also develop retinal pigmentary changes and progressive visual loss.

Cardiac: Cardiac abnormalities include hypertrophic or dilated cardiomyopathy. Pericardial effusion or cardiac failure can lead to death in these patients. FAO disorders with cardiac involvement include carnitine transporter defects, LCHAD, TFP deficiency, neonatal CPT II and VLCAD.

Muscle: There is usually moderate to severe hypotonia with recurrent rhabdomyolysis. Creatinine kinase may be greatly elevated. In infants and children seizures and/or developmental delay may also be present. Rhabdomyolysis is common in the adult form of CPT II, LCHAD, TFP deficiency and VLCAD.

* These are not all the FAO disorders, only the ones thought to be detectable with MS/MS. At this time the sensitivity and specificity of MS/MS to detect all affected infants is unknown.

Mothers carrying an affected LCHAD fetus are prone to developing life threatening acute fatty liver of pregnancy or HELLP syndrome (hemolysis, elevated liver enzymes, low platelets). The reasons for this are not yet understood, but FAO disorders should be considered in children whose mothers have a history of these pregnancy complications.

Treatment

Even with screening, some infants with FAO disorders may die before results are available. Treatment for MCAD and some other FAOs is extraordinarily simple once the diagnosis is suspected. Avoidance of fasting, particularly as infants and young children, is the primary treatment. Carnitine supplementation (100mg/kg/day) is used to provide a pathway for removal of toxic intermediate metabolites in some FAOs. With appropriate treatment

hepatic, cardiac and muscle complications can be reduced or eliminated. Patients with these disorders may require IV support for fluid and calories during intercurrent infections or illnesses. With pre-symptomatic diagnosis and appropriate therapy, outcome can be normal for MCAD. Outcome for the other disorders is unknown.

Screening Practice Considerations

Neonatal forms of FAO disorders can present in the first few days of life. Collect specimens at discharge or between 48-72 hours. Transport within four to six hours of collection and no later than 24 hours after collection. Practitioners must remain alert to the possibility of FAO disorders in any neonate, infant or child with hypoketotic hypoglycemia or "Reyes-like" episodes.

Laboratory Tests

RESULTS	LIKELY CAUSES	ACTIONS
CO (free carnitine) <7.0 μM	<ul style="list-style-type: none"> * Carnitine transport defects possible * Carnitine deficiency * False 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.
C14 (Tetradecanoyl) > 1.0 μM C14:1 (Tetradecenoyl) > 1.4 μM C16 (Palmitoyl) > 9.7 μM	<ul style="list-style-type: none"> * VLCAD possible * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.
C16 (Palmitoyl) > 9.7 μM	<ul style="list-style-type: none"> * LCHAD, VLCAD, CPT II, CT deficiencies possible * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.
C16-OH (Hydroxy Palmitoyl) > 1.1 μM	<ul style="list-style-type: none"> * LCHAD, TFP possible * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.
C6 (Hexanoyl) > 0.9 μM C8 (Octanoyl) > 1.0 μM C10:1 (Decenoyl) > 0.8 μM	<ul style="list-style-type: none"> * MCAD possible * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.
C4 (Butyryl/Isobutyryl) > 1.6 μM	<ul style="list-style-type: none"> * SCAD possible * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.
C4 > 1.6 μM C5 > 1.0 μM C5-DC > 1.7 μM C6 > 1.0 μM C8 > 0.9 μM C10 > 0.9 μM C16 > 9.7 μM	<ul style="list-style-type: none"> * MADD/GA II possible * False positive 	Lab phones results to consultants, who phone practitioner with recommendation. Notification is followed up by mail.

The purpose of newborn screening is to identify infants at risk and in need of more definitive testing. As with any laboratory test, both false negative and false positive results are possible. Screening test results are insufficient information on which to base diagnosis or treatment.

SCREENING PRACTICES

Good screening practices can improve the quality of screening tests and decrease the potential for missing infants with disorders. At least one-third of cases missed by screening programs in the United States are caused by errors in screening practice.

Definition

SCREENING PRACTICES are the actions and decisions of practitioners and birthing facilities regarding the collection and handling of newborn screening specimens. Errors in screening practices can result in delayed identification of infants with disorders, increased morbidity and mortality, delayed intervention/ treatment, and increased medical/legal liability.

Screening Of All Babies

All newborns must be screened, according to the Hawai'i Revised Statutes, Chapter 321-291, and Hawai'i Administrative Rules, Chapter 11-143.

Failure to screen all newborns can result in missed infants with disorders. Most of the affected infants have no family history or clinical symptoms to suggest the disorder. Missed infants with disorders may result in increased morbidity and mortality, higher intervention/ treatment costs, and increased medical/legal liability.

Practitioners are urged to use the term, “newborn screening,” rather than “PKU test,” since other disorders besides PKU are included in the screening battery. Babies with other disorders have sometimes been mistakenly treated for PKU because any abnormal test result was referred to as the “PKU test.”

Responsibility For Screening All Babies

- For hospital births, the hospital and the attending physician or birth attendant are **jointly** responsible for obtaining the newborn screening tests on all infants, unless the tests are refused.
- To assure that all hospital births are tested, hospitals are responsible for monthly summaries of infants born or transferred, whether the newborn screening tests were done, test results, and actions taken based on missing results. The “Hospital Newborn Screening Monthly Report” should be sent to the Hawai'i Newborn Metabolic Screening Program within 30 days after the end of the month.
- For home and non-institutional births, the birth attendant is responsible for assuring that a newborn screening specimen is collected, unless the tests are refused.

Written Refusal For Screening

- Parents, guardians, or other persons having custody or control of the child who refuse newborn screening must sign the special refusal form provided by the Department of Health which includes medical implications.
- A copy of the refusal form should be retained in the infant's medical record and another copy sent to the Hawai'i Newborn Metabolic Screening Program.

Parents, guardians, or other persons having custody or control of the child have the right to refuse newborn screening testing on the basis of their religious tenets and beliefs. If they refuse testing, the special refusal form must be signed. Failure to do so may increase practitioner liability if an affected infant is not screened.

SPECIMEN TIMING		
	If 1st sample is obtained:	then 2nd sample should be obtained
“Early Testing”	<24 hours	≥24 hours -14 days
“Standard Test”	≥24 hours-7 days**	2nd sample is not required if taken by these guidelines

** In any case, a specimen obtained outside the recommended guidelines is preferred over an infant that has no specimen or no repeat at all.

Family Inability To Pay For Screening

- No infant should be refused newborn screening because of the inability to pay.
- Families who cannot afford testing may be referred to the Hawai'i Newborn Metabolic Screening Program for financial assistance with newborn screening.

Proper Time For Testing

- All babies must be screened before discharge from the hospital or by 7 days of age, whichever is sooner, regardless of prematurity, feeding history, illness, hyperalimentation, or antibiotic therapy.
- When a newborn is discharged prior to 24 hours of age, a screening specimen should be collected **as close to discharge** as possible.
- For home and non-institutional births, babies should be tested before 7 days of age.

Specimens should be collected before hospital discharge, since infants may not return for routine pediatric care. Compliance with testing after discharge may be as low as 50-60 percent. Failure to collect a specimen before discharge confers a significant liability on both the facility and responsible practitioner if an affected infant is missed.

Specimens should be obtained for newborns who are discharged early, even though feedings are not well established. Over 95 percent of affected infants have abnormal results on the first test regardless of age or feeding.

Ideally, for optimal testing, an infant should receive normal feedings before the newborn screening specimen is collected. Some protein is needed to unmask the aminoacidopathies but the quantity of ingested protein is not specific. Colostrum, breast milk, and formula have enough protein to detect cases of PKU and MSUD. A galactosemic infant who receives soy formula or intravenous feedings may have a normal blood galactose level, although the Beutler test will detect abnormal enzyme activity unless the infant is transfused.

The optimum time for newborn testing varies with the different disorders. An early test is necessary for disorders which result in neonatal emergencies. All enzyme abnormalities such as biotinidase deficiency, galactosemia, and congenital adrenal hyperplasia, can be detected at birth. At least 90 percent of congenital hypothyroidism can be detected at birth. If the newborn screening test is performed "too early", some cases of

PKU may not be detected because this test measures phenylalanine accumulation. Ten percent of infants with PKU have been missed on the early test because the laboratory failed to detect a minor elevation in the phenylalanine or because the infant had mild PKU.

Although hyperalimentation can result in high levels of several amino acids, this is not a contraindication to newborn screening. This information should be indicated on the specimen collection form.

Repeat Tests For Initial Screens Before 24 Hours Of Age

- If the initial newborn screening specimen is obtained before 24 hours of age, a repeat specimen should be obtained by 14 days of age. (This is an American Academy of Pediatrics newborn screening recommendation.)

This may identify infants with disorders who were missed because the newborn screening test was performed "too early" to detect PKU, since the test measures phenylalanine accumulation. Ten percent of infants with PKU have been missed on the early specimen because the test method is not sensitive enough to detect a minor elevation in the phenylalanine or because the infant had mild PKU.

Screening For Transfused Infants

- Newborn screening specimens should be obtained **before** transfusions.
- If a newborn screening specimen is not obtained before transfusion or dialysis, a specimen should be obtained at the appropriate time when the specimen will reflect the infant's own metabolic processes and phenotype (approximately, 3 days for metabolites; 120 days for enzymes and hemoglobin). Donor blood can dilute plasma levels of metabolites and donor cells can provide normal levels of enzymes and hemoglobins. Metabolite tests (e.g., PKU, MSUD) will become abnormal after feedings are begun, regardless of the transfusion.

Screening For Infants Transferred To Another Hospital

- When possible, the originating hospital should draw a newborn screening specimen **before** transfer of an infant to another hospital.

- If a specimen is not obtained prior to transfer, the **originating hospital** should clearly document this, notify the hospital to which the infant is being transferred, and report this to the Hawai'i Newborn Metabolic Screening Program, using the form "Hospital Report of Newborn Screening Specimen Not Obtained".

Specimen Collection

- The correct specimen collection form must be used, in order for the centralized laboratory to track the infant's results.
 - The 1st Specimen Collection form is used for all initial specimens. (**Hemoglobin screening is done only on the initial specimen.**)
 - The 2nd Specimen Collection form is used for all routine repeat screening on infants whose initial specimens were collected less than 24 hours.
 - The Requested Repeat Specimen Collection form is used for retesting of unacceptable specimens, or for any reason that the testing laboratory is requesting another specimen.
- The laboratory form, which is part of the medical legal record, must be legibly completed with all the information requested. Plastic imprint cards which often produce unreadable information should not be used.
- Complete patient information is critical for locating infants and rapid follow-up in the event of abnormal results. Infant's name, sex, birth date, birth hour, birth weight, gestational age, specimen date and time, mother's name and birth date, primary care physician's name are particularly important. It is also important to indicate what kind of food that the infant has receive prior to testing.
- Specimens should be collected in an appropriate manner.
- Specimens:
 - Must have sufficient blood to do all the tests.
 - Should not be contaminated with milk, stool or urine.

- Should not be heated during specimen drying or mailing. Heat diminishes enzyme activity.
- Should not be taken from the intravenous line which is used to deliver hyperalimentation.
- Should **not use cord blood**. Cord blood does not measure the infant's capacity to metabolize protein or galactose, and the results may be affected by maternal enzymes which cross the placenta. Cord blood is therefore not an acceptable specimen for PKU, MSUD, or disorders detected by tandem mass spectrometry.

Specimen Transport

- All newborn screening specimens should be mailed within **24 hours** after collection, whenever possible.
- Specimens should be received by the central newborn screening testing laboratory no later than **five days** after collection.
- Specimens should be mailed once a day except when mailing service is unavailable on weekends or on holidays. Prompt mailing is essential to reliable testing. Specimens which are received by the screening laboratory later than 10 days after collection may have diminished enzyme activity.

Clinical Signs and Symptoms

- If signs and symptoms of one of the newborn screening conditions are clinically evident, the physician should contact a metabolic center or metabolic physician for assistance with diagnostic testing and treatment, pending the results of the screen.
- If clinical symptoms suggest one of the screened conditions despite a "normal" screening test result, the physician should immediately contact a consultant specialist for instructions on further evaluation of the patient.
- For some disorders, like medium chain acyl-CoA dehydrogenase deficiency (MCADD), detection by MS/MS is reliable and early treatment is simple and efficacious. Unfortunately, the incidence and efficacy

of early diagnosis and treatment for many of the other disorders is unavailable or unproven. As with all conditions, there may be false negative results and practitioners should remain alert for signs of these conditions in infants and children regardless of screening results. Conversely, false positives are possible.

Family History

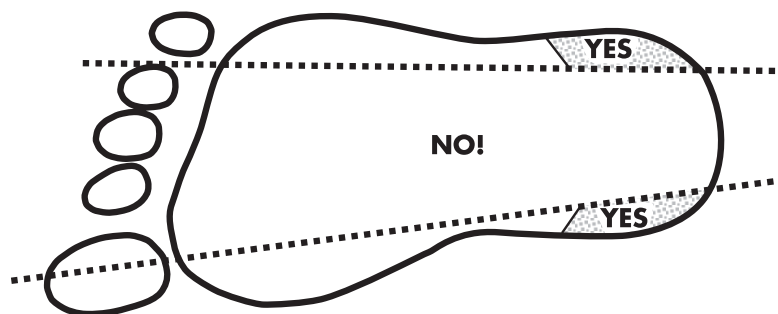
- For any infant with a positive family history, the physician should contact appropriate consultant specialists, ideally prenatally, or immediately at birth, to determine the proper diagnostic tests and proper timing of those tests.

Consultation with a specialist is usually necessary and always recommended in these situations. The directory on pages 1 and 2 offers consultants by disease for your state to assist with screening and confirmation testing.

SPECIMEN COLLECTION PROCEDURES

1. To prevent specimen contamination, do not touch any part of the filter paper circles before, during or after collection. Disposable gloves and powdered lactose residue can contaminate the specimen.
2. Samples obtained from the heel and dorsal hand vein are acceptable. **Cord blood is not an acceptable specimen.** Samples obtained from peripheral or central line are acceptable, provided that the line is not being used for hyperalimentation.
3. For heel puncture:
 - Hold infant's limb lower than the heart, warm if necessary with water or a warm towel. Heat pack should not exceed 42° C and should not be left in contact with the skin for a prolonged period.
 - Select a puncture site on the heel (see diagram) and cleanse with alcohol (not iodine), air dry.
 - Puncture the heel with the sterile lancet to the full length of the blade. Wipe away the first drop of blood to remove tissue fluids. Sufficient blood should collect on the heel to fill each circle by a single application of paper to a drop of blood. Apply only from one side of the filter paper. Blood should soak all the way through the paper such that the blood spots look similar on both sides. **Complete saturation of the entire circle is essential for accurate testing.**
4. It is important **not** to superimpose the blood drops on top of each other. Let each drop touch the paper about 1/8 inch away from the previous one. This prevents layering of blood on the paper, which is one cause of false results.
5. **Collect the blood in all five circles.** A minimum of four circles is necessary to complete the test battery. If there are problems obtaining an adequate quantity of blood, it is better to fill four circles completely, than to fill five circles inadequately.
2. Air dry the blood specimens at room temperature for 2-4 hours in a horizontal position. Do not dry on a heater or microwave. Ensure that sample is completely dry before mailing.
7. Insert dried sample into envelope (do not use plastic bags), seal and **mail to the testing laboratory within 24 hours of collection. Do not batch specimens collected on separate days.** If sample cannot be mailed because of the weekend or holiday, it is better to store it in a cool room and send by standard overnight express mail on the next available mailing day.

Recommendation for Heel Puncture Site in Newborns



Perform punctures on the most medial or most lateral portion of the plantar surface of the heel (see diagram). Lancets longer than 2.4 mm should not be used on infants weighing less than 2500 g. Specimen collection procedures shall follow the National Committee for Clinical Laboratory Standards, "Blood Collection on Filter Paper for Neonatal Screening Programs", NCCLS Document LA4-A2.

¹These instructions are consistent with the recommendations in *Blood Collection on Filter Paper for Neonatal Screening Programs. National Committee for Clinical Laboratory Standards. Vol. 12 No. 13 1992 [NCCLS Document LA4-A2]*

MOST COMMON ERRORS IN SPECIMEN COLLECTION

INVALID SPECIMEN	POSSIBLE CAUSES
Quantity of blood not sufficient for testing (QNS)	Filter paper circles incompletely filled or not saturated/not all circles filled. Blood applied with needle or capillary tube. Contamination of surface of filter paper circle before or after specimen collection by gloved or ungloved hands, or by substances such as hand lotion or powder, etc.
Blood spots appear scratched or abraded	Blood applied improperly using capillary tube or other means (blotter has been damaged or torn by device).
Blood spots wet	Specimen not properly dried before mailing.
Blood spots appear supersaturated	Excess blood applied (usually with capillary tube or needle). Blood applied to both sides of filter paper.
Blood spots appear diluted, discolored, or contaminated	Puncture site squeezed or “milked.” Exposure of blood spots to direct heat. Contamination of filter paper before or after specimen collection by gloved or ungloved hands, or by substances such as alcohol, formula, water, powder, antiseptic solutions, or hand lotion. Contamination during transit.
Blood spots exhibit “serum rings”	Alcohol not wiped off puncture site before skin puncture is made. Filter paper has come into contact with alcohol, water, hand lotion, etc. Puncture site squeezed excessively. Specimen dried improperly. Blood applied to the filter paper with a capillary tube.
Blood spots appear clotted or layered	Same filter paper circle touched to a blood drop several times. Circle filled from both sides of the filter paper.
Blood will not elute from the blotter paper	Blood specimen has been heat-fixed. Blood specimen is too old (more than two weeks between collection and receipt by the screening laboratory).

Consult the state screening lab for additional information and assistance with specimen collection.

A full-color chart illustrating invalid specimens and their causes, “Simple Spot Check,” may be obtained at no charge from Schleicher & Schuell, Inc., PO Box 2012 Keene, New Hampshire 03431; 800-245-4024; FAX 603-357-7700.

PROBLEMS IN SCREENING PRACTICE

In the United States a few common screening problems occur in every state. The central newborn screening testing laboratory and the state newborn screening program have developed a quality control program to assist practitioners and hospital administrators with these problems. Components of this program include ongoing education of practitioners and parents, computerized monitoring of specimens received, and documentation of problems associated with mail delays.

Infants Who Are Never Tested

Nationwide, newborn screening programs are unable to test one percent of the infants. Statistically, these numbers represent three cases of PKU and ten cases of hypothyroidism which are likely to be missed each year. These infants represent a major medical and legal liability to the program and to practitioners involved in their care. The legal awards for missed cases have been as high as \$30 million per case.

Parents' Refusal To Have The Baby Tested

See page 34 for guidelines, and page 46 for an example of form to use in this situation.

Common Misconceptions

Misconceptions about newborn screening disorders or "proper time to test" can lead to failure to test an infant and undermine the effectiveness of a newborn screening program. Two common misconceptions include:

1. Practitioner advice to parents that the diseases are so rare that testing is not necessary. Approximately 30-40 infants are identified each year in the Northwest Regional Newborn Screening Program. Most of the affected infants have no family history or clinical symptoms to suggest the disorder.
2. Practitioner belief that the first test is invalid if obtained prior to 24 hours of age or prior to established feedings. Over 95 percent of affected infants have abnormal results on the first test regardless of age or feeding. Postponing the first test until after discharge should not be condoned.

Timing Of The Tests

The trends toward early hospital discharge and renewed interest in home deliveries complicate the management of newborn screening. The "best age" to do testing is a problematic issue still under debate.

Hawai'i Administrative Rules state that "all infants shall have a newborn screening specimen drawn before discharge from the hospital, or by seven days of age, which ever comes first, and sent to the designated laboratory". If an infant is to be discharged prior to 24 hours of age, a newborn screening specimen should be collected as close to discharge as possible, regardless of age and feeding history. If the initial newborn screening specimen is obtained before 24 hours of age, then a repeat specimen should be obtained before 14 days of age, according to the American Academy of Pediatrics newborn screening recommendations.

Unacceptable Specimens

Approximately one percent of newborn screening specimens submitted to the central newborn screening testing laboratory contain insufficient blood to do all the tests or are contaminated with milk, stool or urine. Newborn screening specimens which are heated during drying or mailing may be damaged and may have invalid results. Enzyme activity may be diminished in specimens which are received by the screening laboratory later than 10 days after collection or which have been exposed to heat and humidity.

Inadequate Demographic Information

Ten percent of specimens received by the central newborn screening testing laboratory are missing key patient information. The newborn screening specimen collection forms should be filled out completely. In the event of an abnormal result, locating the infant without key information is difficult and time consuming. The most common cause of unreadable specimens is the use of imprinting machines which use plastic cards to stamp the infant's name on the request. Data which are critical include: name, birth date/hour, sample date/hour, birth weight, feeding status, as well as the practitioner's name.

Problems Related To Specimen Transport To The Laboratory

All newborn screening specimens should be mailed within **24 hours** after collection. Specimens should be mailed once a day except when mailing service is not available on weekends or on holidays. Specimens should be received by the central newborn screening testing laboratory no later than **five days** after collection. Newborn screening specimens may be delayed

because of in-house mail systems. To discourage “batching” specimens over several days before mailing, the Hawai‘i Newborn Metabolic Screening Program is contracting with a mail courier service to provide “overnight mail” service to all birthing facilities.

Prompt mailing is essential to reliable testing.

Specimens which are received by the screening laboratory later than 10 days after collection may have diminished enzyme activity.

REPORTING OF AND FOLLOW-UP OF RESULTS

Responsibilities

It is the **joint** responsibility of the hospital and practitioner or birth attendant to ensure that every infant is tested, that a result is received, and that appropriate follow-up is provided.

Documentation of Specimen Collection and Receipt of Test Results

Specimen collection must be documented in the infant's chart. Information should include name of infant, screening kit ID number, date collected, date mailed and the name of the person who collected the specimen. When screening results are returned to the submitter, results should be noted in the log book and the report filed in the medical records.

Missing Test Results

If the infant's screening test result is not received from the Oregon State Public Health Laboratory (OSPHL) within two weeks after collection, the hospital and practitioner **must** assume responsibility for follow up. The following procedure is recommended:

1. Contact the Hawai'i Newborn Metabolic Screening Program at (808)733-9069; or the Oregon State Public Health Laboratory, Newborn Screening Section, Leanne Rien, RN, Coordinator, (503)229-5466, to determine if the specimen was received and to request a report.
2. If the specimen was not received, it should be presumed lost. Notify the infant's primary care practitioner or parent that the specimen may have been lost and that another specimen should be obtained without delay. Document this action in the infant's medical record.
3. If the infant cannot be retested, notify the Hawai'i Newborn Metabolic Screening Program at (808)733-9069.

Normal Results

Normal results are mailed daily to the newborn screening specimen submitters and to the primary care

practitioners. The complete test battery is usually completed within seven working days after the specimen is received by the laboratory.

"Significant" Abnormal Results

All significant abnormal test results are considered urgent and are reported by telephone and facsimile. OSPHL will contact the Oregon medical consultants and the Hawai'i Newborn Metabolic Screening Program. The Oregon medical consultant will contact the primary care practitioner by phone and the Hawai'i medical consultant, if requested by the primary care practitioner. The Hawai'i Newborn Metabolic Screening Program will fax the test results to the practitioner. Confirmation of test results and recommendations are mailed.

"Other Abnormal and Repeats"

OSPHL will send a letter to the submitting hospital and/or practitioner with a request for retesting on lesser abnormalities and/or unacceptable specimens.

It is the practitioner's responsibility to ensure that any infant with abnormal results is retested. Pending results are tracked by the laboratory and the Hawai'i Newborn Metabolic Screening Program until resolution or confirmation.

Confirmation Testing

The practitioner caring for an infant with a positive newborn screening test is responsible for ordering confirmatory tests. The practitioner may request assistance from the Hawai'i Newborn Metabolic Screening Program if the physician has difficulty contacting the family regarding the positive newborn screening test result and the need for confirmatory testing.

When the practitioner orders tests requested by Oregon State Public Health Laboratory, following OSPHL instructions, families do not incur costs for the tests. Families, however, are responsible for any laboratory charges for specimen collection and handling. Families are also responsible for the costs of the tests which are not requested by OSPHL.

EDUCATIONAL SERVICES

Educational services and consultation are provided upon request by the Hawai'i Newborn Metabolic Screening Program, in collaboration with the Oregon State Public Health Laboratory, the Oregon Health and Science University, and the Hawai'i medical consultants.

Screening Practice Surveillance Profiles

In an effort to assist hospitals monitor newborn screening practices, the Hawai'i Newborn Metabolic Screening Program will provide Screening Practice Profiles to birthing facilities in Hawai'i.

Birthing Facilities, Laboratories, And Community Practitioners

1. Inservice sessions about the newborn screening system can be provided by the Hawai'i Newborn Metabolic Screening Program staff.
2. Policy development and/or review. Hawai'i Newborn Metabolic Screening Program staff are available to assist administrators and/or practitioners in the drafting of screening policies and

procedures based on State laws, administrative rules as well as recommendations of the American Academy of Pediatrics and the National Committee for Clinical Laboratory Standards. This can be done in conjunction with inservice sessions or by mail or phone.

3. Video tape demonstrations showing correct collection procedures.

Parents And Lay Public

1. Parent brochures are included with each kit order.
2. Video tapes are available to answer basic questions about the screening tests. Appropriate for both pre- and postnatal education.

There is no charge for any of these educational materials or services. For additional information please contact:

Hawai'i Newborn Metabolic Screening Program
741 Sunset Avenue
Honolulu, HI 96816
PHONE: (808)733-9069
FAX: (808)733-9071

SPECIMEN COLLECTION FORMS, COST, AND MAILING

1st Specimen Collection Form

Purpose:	<p>For initial newborn screening testing panel.</p> <p>Only a standardized, quality tested filter paper (Schleicher and Schuell 903) can be used for specimen submission.</p>
Cost:	<p>\$47.00 per kit. The kit consists of the specimen collection form, envelope, and parent information brochure.</p> <p>The cost includes the cost for initial newborn screening and, if requested by OSPHL, repeat and confirmatory testing. The cost includes mailing for the initial specimen.</p> <p>The cost excludes specimen collection and handling. The cost excludes mailing for repeat and confirmatory specimens.</p>
How to order:	<p>Use the kit request form showing the quantity requested. It must include a purchase order or check for prepayment. Orders should be submitted to:</p> <p style="padding-left: 40px;">Hawai'i Newborn Metabolic Screening Program 741 Sunset Avenue Honolulu, HI 96816 Phone (808)733-9069 FAX (808)733-9071. Allow 14-21 days for preparation and shipping.</p> <p>Forms are precoded for the specific individual/facility. Therefore, forms should NOT be loaned to, or borrowed from, other facilities.</p>
Replacement:	<p>Damaged or unusable forms due to transfer, expiration, or refusal, may be replaced by sending these forms to:</p> <p style="padding-left: 40px;">Hawai'i Newborn Metabolic Screening Program 741 Sunset Avenue Honolulu, HI 96816</p> <p>New 1st Specimen Collection forms will be issued, at no cost, upon receipt of the damaged or unusable forms.</p>

2nd Specimen Collection Form

Purpose:	For repeat testing for initial specimens collected <24 hours of age. 2nd Specimen Collection Forms should not be used for initial screening specimens.
Cost:	None. The cost is included in the cost for the 1st Specimen Collection Form.
How distributed:	Hawai'i Newborn Metabolic Screening Program sends form to primary care practitioner when a specimen is requested. A supply of 2nd Specimen Collection Forms will also be distributed to all the birthing facilities at no charge.

Requested Repeat Form

Purpose:	For repeat test on the unacceptable specimens, borderline positives, or any other reason requested by OSPHL.
Cost:	None. The cost is included in the cost for the 1st Specimen Collection Form. OSPHL absorbs the costs of these tests when the tests are requested by OSPHL, specimens are properly handled, and specimens are submitted to OSPHL or the specified OSPHL-contracted laboratory. Note: Costs for tests which are not specifically requested, or which are sent to other laboratories, will not be reimbursed.
How distributed:	OSPHL sends form to primary care practitioner when a specimen is requested.

Requests for Forms for Urgent Situations

Contact the Hawai'i Newborn Metabolic Screening Program at (808)733-9069 to obtain uncoded kits for situations when forms are **urgently** needed.

Specimen Mailing

All initial specimens should be sent by the "overnight mail" service contracted by the Hawai'i Newborn Metabolic Screening Program. There is no additional cost to the birthing facilities for this service. Specimens should be mailed once a day except when mailing service is unavailable on week-ends or on holidays. The Hawai'i Newborn

Metabolic Screening Program will not pay for mailing when a non-contracted mail service is used.

The Hawai'i Newborn Metabolic Screening Program does not pay for mailing for repeat or confirmatory specimens.

Mailing Address

All initial and repeat screening specimens must be sent to the Oregon State Public Health Laboratory for testing, P.O. Box 275, Portland, OR 97207-0275.

Confirmatory specimens should be mailed to the contracted laboratory designated by OSPHL at the time of physician notification of test results.

REFUSAL OF NEWBORN SCREENING TESTS_____
Name of Infant_____
Place of Birth_____
Birth Date_____
Street Address_____
Medical Record Number_____
City/State/Zip

I have received the parent informational brochure entitled, "Testing Your New Baby for Hidden Birth Defects," concerning the newborn screening tests for phenylketonuria (PKU), congenital hypothyroidism, congenital adrenal hyperplasia (CAH), maple syrup urine disease (MSUD), galactosemia, biotinidase deficiency, hemoglobin disorders, other amino acid disorders, urea cycle disorders, organic acid disorders, and fatty acid oxidation disorders.

I have been informed and I understand that these tests are required by State law for all infants born in Hawai'i.

I have been informed and I understand that these tests are given to detect these disorders as symptoms may not appear for several weeks or months.

I have been informed and I understand that, if untreated, these conditions may cause permanent damage to my child, including serious mental retardation, growth failure, and even death.

I have been informed and I understand the nature of these tests and how these tests are given.

I have discussed this test with _____ and I understand the risks involved if these tests are not given to my child.

I object to these tests and refuse to have my newborn child tested on the ground that these tests conflict with my religious tenets and beliefs.

My decision was made freely without force or encouragement by my doctor, hospital personnel, or any State official.

Parent's or Legal Guardian's Name (Print)_____
Parent's or Legal Guardian's Signature_____
Witness' Signature_____
Date

NBS 9/03

White Copy: Infant's Medical Record

Yellow Copy: DOH/NBS

Pink Copy: Parent

Newborn Metabolic Screening Program
Hawai'i State Department of Health
741 Sunset Avenue, Honolulu, HI 96816
Phone: (808) 733-9069 Fax: (808) 733-9071

NEWBORN METABOLIC SCREENING KIT ORDER FORM

The Revised Hawai'i Administrative Rules, Chapter 11-143, requires a payment of \$47.00 for each initial newborn screening kit, effective September 1, 2003.

INSTRUCTIONS

1. Complete this order form to ensure correct processing of your request for newborn screening kits. Each kit includes a newborn screening specimen collection form, a parent information brochure and an envelope.
2. Mail or fax this order form to: State of Hawai'i
Newborn Metabolic Screening Program
741 Sunset Avenue
Honolulu, HI 96818
Ph. (808) 733-9069 FAX (808) 733-9071
3. If using a purchase order, submit your payment (check or money order) with a copy of the invoice to the above address. Make the check or money order payable to **Director of Finance**.

Facility Name: _____	Submitter Code: _____
Department/Section: _____	Contact Person: _____
Street Address: _____	
City/State/Zip Code: _____	
Telephone Number: _____	Fax Number: _____
Purchase Order #: _____ Quantity of Kits: _____ X \$47.00 = \$ _____ Total cost	
Quantity of salmon striped envelopes _____ Quantity of manila envelopes: _____	

Please allow two to three weeks for delivery. Call the Newborn Metabolic Screening Program at (808) 733-9069 for assistance or if you have any questions.

NBMSP USE ONLY

Date Request Received: _____ Date Request Sent to OSPHL: _____

OSPHL USE ONLY

Date Request Received _____ Date Order Shipped: _____
 Order Packed by: _____ Order Reviewed by: _____
 Kit Numbers: _____

Place Bar Code Here Verified (OSPHL USE ONLY) _____

Rev. 6/5/03

HAWAII DEPARTMENT OF HEALTH

[PART XX11.] NEWBORN METABOLIC SCREENING

§321-291 Tests for phenylketonuria, hypothyroidism, and other metabolic diseases.

(a) The department of health may specify diseases to be screened for in newborn infants and methods to be employed to best prevent mortality and morbidity within the population of the State.

(b) The person in charge of each institution caring for newborn infants and the responsible physician attending the birth of a newborn or the person assisting the birth of a child not attended by a physician, shall ensure that every infant in the person's care be tested for phenylketonuria, hypothyroidism, and any other disease that may be specified by the department of health; provided that this section shall not apply if the parents, guardians, or other persons having custody or control of the child object thereto on the grounds that the tests conflict with their religious tenets and beliefs, and written objection is made part of the infant's medical record.

(c) The department of health shall adopt rules pursuant to chapter 91 necessary for the purposes of this section, including, but not limited to:

- (1) Administration of newborn screening tests:
- (2) Quality and cost control of screening tests:
- (3) Retention of records and related data:
- (4) Reporting of positive test results:
- (5) Guidelines for care, treatment, and follow up of infants with positive test results:
- (6) Informing parents about the purposes of these tests; and
- (7) Maintaining the confidentiality of affected families.

(d) There is created in the treasury of the State the newborn metabolic screening special fund. All moneys for newborn metabolic screening services collected under this chapter shall be deposited in the newborn metabolic screening special fund to be used for the payment of its lawful operating expenditures, including but not limited to laboratory testing, follow-up testing, educational materials, continuing education, quality assurance, equipment, and indirect costs.

(e) The director shall submit an annual report to the legislature twenty days prior to the convening of each regular session, identifying all fund balances, transfers, and expenditures made from the newborn metabolic screening special fund, and the purposes for each expenditure.



A COLLABORATIVE PROJECT INVOLVING:

OREGON DEPARTMENT OF HUMAN SERVICES

OREGON HEALTH & SCIENCE UNIVERSITY

ALASKA DEPARTMENT OF HEALTH & SOCIAL SERVICES

STATE OF HAWAII DEPARTMENT OF HEALTH

IDAHO DEPARTMENT OF HEALTH & WELFARE

NEVADA STATE HEALTH DIVISION



In compliance with the American with Disabilities Act (ADA), if you need this information in alternate format, please call: Oregon State Public Health Laboratories at (503) 229-5882.

**<http://www.ohd.hr.state.or.us/nbs/index.cfm>
<http://www.oregon.gov>**